

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
MEDICAL TOXICOLOGY BRANCH  
SUMMARY OF TOXICOLOGY DATA

LITHIUM HYPOCHLORITE

SB 950-051, Tolerance # 50243

September 28, 1987

Revised: 3/14/89, 10/23/91

I. DATA GAP STATUS

Chronic rat:	Data gap, no study on file <sup>1</sup>
Chronic dog:	Data gap, no study on file <sup>1</sup>
Oncogenicity rat:	Data gap, no study on file
Oncogenicity mouse:	Data gap, no study on file
Reproduction, rat:	Data gap, inadequate study, possible adverse effect indicated
Teratology rat:	No data gap, no adverse effect <sup>2</sup>
Teratology rabbit:	Data gap, inadequate study, no adverse effect indicated
Teratology mouse:	Data gap, inadequate study, possible adverse effect
Gene mutation:	No data gap, no adverse effect

Chromosome Effects: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotoxicity: Not required at this time

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1Submitted information includes reviews discussing human case history and epidemiology data, as well as copies of many published reports cited in those reviews. There are some animal data describing short term and chronic effects of lithium. These data do not fill chronic data gaps. (Aldous, 10/23/91).

2Note that lithium carbonate and lithium citrate are listed under "Proposition 65" as "known to the State to cause reproductive toxicity" [specifically developmental toxicity]. The basis of this listing is the FDA requirement that package inserts for these products bear specific warnings to women of childbearing age. Aldous, 10/23/91.

**Note, Toxicology one-liners are attached**

Note: these pages contain summaries only. Individual worksheets may identify additional effects.

File name: T911023 Revised: 10/23/91

All studies on file as of 8/29/91 with prospects of filling data gaps under FIFRA were included in this review. Critical ancillary studies were also included. Some reviews, case reports, and reports of miscellaneous studies were not selected for inclusion in this Summary. Records up to 092291 (Document 50243-020) have been examined. Aldous, 10/23/91.

Note: In the 1-liners below:

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

Note: For the purpose of filling data gaps, CDFA has grouped lithium hypochlorite with calcium hypochlorite (SB-028) and sodium hypochlorite (SB-866). Studies have been submitted for both calcium hypochlorite and lithium hypochlorite. It was the intent of CDFA Medical Toxicology Branch that the toxicity of lithium, as well as that of the hypochlorite anion, be evaluated. This Summary, therefore, contains studies on lithium hypochlorite as well as on other salts of lithium.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

### CHRONIC

No acceptable chronic animal studies have been submitted. Since lithium salts such as the carbonate have been used extensively for over 3 decades for manic depressive illness, an impressive array of human data has accumulated. The therapeutic index of lithium is very small and treatment often encompasses many years of continuous exposure at the low end of a rather steep dose-response curve. Human exposure histories are thus the most promising sources of chronic toxicity data. Lithium is rapidly absorbed after oral dosing, and is cleared from the body rather rapidly, and many of the findings noted in the course of chronic therapy are comparable to responses of acute exposure. Having examined the human and animal chronic data in the submitted volumes, this reviewer (Aldous) does not find sufficient information to demonstrate in man or to predict from animal data a chronic NOEL for man for chronic effects. Also, the effect(s) which would define the corresponding LEL are not presented. Thus data requirements for rodent and non-rodent chronic studies remain. Aldous (10/23/91).

There are several reviews in Document 50243-020, and information from one of them is included below. Following that are excerpts from a recent Physicians' Desk Reference (PDR). The PDR tends to list virtually all effects attributed to therapeutic exposure, whereas the majority of reviews by practicing clinicians emphasize the more characteristic responses at

therapeutic levels. There are additional reviews, including several by key investigators with extensive clinical experience with lithium. Some of the major reviews are presented as appendices to the petition by Foote Mineral Co. to the Pennsylvania Department of Environmental Resources regarding final effluent limits for lithium and bromide at a plant in Frazer, PA (beginning p. 000295 in Document 50243-020). The Foote data are potentially relevant here because the levels of potential exposure are comparable to what might be obtained from treated swimming pools (i.e. a few mg Li/person/day in "worst-case" conditions, compared to therapeutic doses on the order of 200 mg Li/person/day). One of the weak points in the presentation of chronic data in this volume is that there is not a clear presentation of dose-effect relationships at the lower end of the therapeutic range. The closest that the data come to identifying apparent "LELs" for human toxicity during chronic therapeutic exposure is a report by Schou and Thomsen entitled "Report submitted to Mr. Arthur S. Gillespie, Lithium Corporation of America", (1981), Document 50243-020, Record No. 092245, beginning p. 001065 of this document. On p. 1066, they state: "Although to our knowledge no effects of lithium have ever been observed in any person at 12-hour serum concentrations below 0.3 mmol/l, . . ."

Although Medical Toxicology Branch does not have data to fill the chronic data gaps, some of the common clinical effects which might be observed at or near to the LEL might include subjective reporting of "thirst", polyuria, and fine tremor. Major organs or tissues affected might include kidneys, thyroids, and hearts. Hematologic effects would possibly involve leukocytoses. Changes in thyroid hormone levels could be expected among clinical chemistry effects. To date, the human data presented are not sufficient to demonstrate dose-response over the range of therapeutic effectiveness down to an apparent NOEL. It is perhaps not realistic to expect such human data to be available, since therapeutically effective doses are in the low end of the range of chronic toxicity, whereas sub-therapeutic doses are of no clinical interest. Aldous, 10/23/91.

50243-020 092202 Dempsey, G.M., and Meltzer, H.L., "Lithium toxicity: A review", in Neurotoxicology, Roizia, L., Shiraki, H., and Greevic, N., eds.; Raven Press, NY, pp. 171-183 (1977). [References to page numbers in this CDPR summary are page numbers from the original

publication: the copy included in this Vol. -020 begins on p. 000248]. Acute toxicity human data: one elderly woman died from apparent lithium poisoning following ingestion of about 100 meq lithium (i.e., about 700 mg Li). Symptoms in this case and in other serious cases involved "tremor, muscle twitches, apathy, and difficult mentation and progressed to blurring vision, confusion, restless coma, and in two cases, death". An investigator (Cleveland) took 8 g of LiCl (apparently a total of 1.3 g of lithium, about 6 times therapeutic levels) in four divided doses over 28 hr, and suffered from many of the above symptoms, plus staggering gait. Symptoms lasted for as long as 5 days. Serum levels in patients maintained on lithium in Sweden were typically well controlled (according to Allgen, cited in this review): only 4 of over 1,000 patients (sampled periodically for a total of 20,000 analyses) had serum levels over 2.0 meq/L. All of these 4 were older patients having management problems associated with dementia (hence misdosing may have occurred). The highest serum level recorded was 3.6 mEq/l. All patients survived. Schou et al. were cited (a 1968 publication, on p. 172 of the review) in an analysis of 8 human poisonings. Moderate increases in blood creatinine and/or b.u.n. were noted in most patients, and these increases were usually reversible. Abnormal T waves were noted in EKGs of 4 of these patients. Schou et al. noted that in humans the CNS is more affected than kidney or heart, unlike relative organ toxicity in some experimental animals (p. 173). He characterized severe lithium intoxication as "dominated by severe and protracted impairment of consciousness", like barbiturate intoxication except that lithium increases deep tendon reflexes and muscle tone, and lithium does not flatten the EEG (but may decrease alpha activity and increase theta and delta activity). Permanent neurological effects including tremors and ataxia have been observed in some patients (p. 174). Often phenothiazines were part of the drug regimens to which such patients had been exposed, in addition to lithium. Three healthy volunteers were administered 50 mEq Li/day [about twice the therapeutic dose] for 1 to 3 weeks, and reported "passivity, a subjective sense of indifference, and a feeling of being at a distance from events" (p. 175). Lithium uptake into brain is slow: in a rat study, brain levels were still increasing when plasma levels were already decreasing after a single dose (p. 175). This delay in peak brain levels was indicated by the author as a possible reason for clinical reports of CNS symptoms such as slurred speech in patients whose lithium levels had dropped below the range of toxicological concern. Lithium excretion is almost exclusively via urine, and lithium clearance is only about 20% of creatinine clearance

(p. 176) due to tubular reabsorption. Excretion is enhanced by a number of chemicals, including sodium bicarbonate. Diabetes insipidus is frequently noted in humans at normal therapeutic dosages, without a clear dose-response (p. 177): Forrest et al. found that 40% of patients on lithium therapy reported "subjective increase in thirst", and polyuria (defined as > 3 l/day) was documented in 12% of patients. Various investigators, including Baer et al. (see pp. 177-178) have found that thiazides, which are diuretics which inhibit sodium reabsorption in the tubules, have the effect of lowering serum sodium and raising serum lithium. In fact, Himmelhoch et al. (p. 178) have found that thiazides can be used successfully to maintain therapeutic concentrations of lithium in the blood. Aldous, 9/30/91 (no Medical Toxicology Branch worksheet, since the article is a review).

50243-020 092205 Fieve, R.R. and Peselow, E.D. (1985). "Lithium Toxicology". Current Applications in Science, Medicine, and Technology, Bach, R.O., ed; John Wiley and Sons, NY, pp. 353-375. This is another reasonably recent, balanced, and very readable review like 092205, above. This record should also be consulted if additional chronic toxicity data are submitted. (No Medical Toxicology Branch "review" of this review at this time). Aldous, 10/8/91.

Physicians' Desk Reference (PDR 44 Edition, 1990), pp. 2100-2102, discusses the Smith Kline & French  $\text{LiCO}_3$  product, Eskalith. The description begins with the warning: "Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy". Use warnings note the occasional presence of "nephrogenic diabetes insipidus, with polyuria and polydipsia", which is usually reversible when treatment is discontinued. Warnings also note that "Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphogenic change have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal functional and morphologic changes and their association with lithium therapy have not been established." Progressive or sudden renal functional changes are indications that lithium therapy should be re-evaluated. Expected adverse reactions at therapeutic levels [typical dose is 900 mg  $\text{LiCO}_3$ , or 147 mg lithium/day for maintenance]

include "hand tremor, mild thirst, and polyuria": these symptoms sometimes persist throughout treatment. "Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration": if such effects do not soon subside, lithium therapy may need to be discontinued. Toxic effects which might occur at lithium levels on the order of 2 mEq/l include "Diarrhea, vomiting, drowsiness, muscular weakness, and lack of coordination". The "Adverse Reactions" section provides a rather long list of reported reactions:

"The following reactions have been reported and appear to be related to serum lithium levels, including levels within the therapeutic range:

**Neuromuscular/Central Nervous System** -- tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreo-athetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes; **Cardiovascular** -- cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction, with severe bradycardia (which may result in syncope); **Gastrointestinal** -- anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion; **Genitourinary** -- glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst, and polydipsia; **Dermatologic** -- drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angioedema; **Autonomic** -- blurred vision, dry mouth, impotence/sexual dysfunction; **Thyroid Abnormalities** -- euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower  $T_3$  and  $T_4$ . I131 uptake may be elevated. (See Precautions.) Paradoxically, rare cases of hyperthyroidism have been reported; **EEG Changes** -- diffuse slowing, widening of the frequency spectrum, potentiation and disorganization of background rhythm; **EKG Changes** --

reversible flattening, isoelectricity or inversion of T-waves; **Miscellaneous** -- fatigue, lethargy, transient scotomata, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, dental caries. Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypothyroidism which persist after lithium discontinuation have been received."

#### CHRONIC RAT

No study on file.

#### CHRONIC DOG

No study on file.

#### ONCOGENICITY

A few isolated reports, usually by clinicians, have indicated a possible association of lithium with leukemias. To date only scant epidemiological analyses of available human tumor incidence data have been performed. One such evaluation was done by Norton and Whalley (see one-liner below). In the latter sample, only 33 persons had died during the study timeframe, and only 4 of those had cancers listed as cause of death (none of them leukemias). Incidental cancers were not identified in that report. Obviously, much more extensive studies than that one would be required in order to provide any meaningful tumor incidence data for risk assessment. More time has passed since the above epidemiological reports were presented. Many more individuals have died following prolonged, documented lithium exposure; therefore there may be much more substantive epidemiological data available now than were presented in the above reports. Nevertheless, due to the fact that human death certificates do not ordinarily provide tumor data except when tumors are probable cause of death, it seems



unlikely that human data would be obtainable of sufficient quality to warrant waiving oncogenicity studies. **Therefore, animal oncogenicity studies will be required unless satisfactory human epidemiological data can be provided.** Aldous, 10/23/91.

Although a one-liner below representing a collection of leukemia case reports is boldfaced, the overall hazard assessment for oncogenicity risk for lithium does not indicate a "possible adverse effect" at this time: instead one must conclude that the overall data are far from adequate to assess oncogenic risk. Aldous, 10/23/91.

#### **HUMAN DATA, INCLUDING EPIDEMIOLOGY DATA**

50243-020 092241 Norton, B. and Whalley, L.J., "Mortality of a lithium-treated population", Br. J. Psychiatry 145:277-282 (1984). Health records were searched for 791 subjects who were treated with lithium for at least 2 months in south-east Scotland over the timeframe 1967-1976. As of July, 1977, 33 of these were dead. Of these, 8 were suicides (far above expected numbers in the general population, and not unexpected among persons suffering from manic-depressive illness), and 14 cardiovascular deaths (11 due to myocardial infarction: significantly above the expected number of cardiovascular deaths, 6.5). There were no other causes of death (including cancers), which appeared to be related to treatment. Investigators concluded that lithium exposure may have played a part in the cardiovascular deaths, however they noted that complex predisposing factors related to the underlying disease (or its treatment) may have been the major factors. No Medical Toxicology Branch worksheet, since this is not a required study. Aldous, 9/27/91.

**50243-020 092213-092215** (Five "case reports" associating lithium therapy with either aplastic anemia, acute monocytic leukemia, acute myeloid leukemia, acute myeloblastic anemia, or megaloblastic anemia). Reports are found on pages 000537-000546, and include record numbers 092213-092215 [not every case report was assigned a record number]. An additional related record (#092210) is found on pp. 000525-000526. These references were apparently the 5 cases reviewed by Dr. William Greaves (p. 000536, this volume), who determined that "These case

reports most certainly do not indicate a cause and effect relationship between lithium carbonate and leukemia in general". The 5 case reports are followed [beginning on p. 000547 under Record No. 092216] by an interpretation by Dr. Paul Leber in Psychopharmacology Bulletin 17:10-12+(incomplete copy)(1981). Dr. Leber discusses the limitations of inferences which could reasonably be made using cohort or case-control analyses. It appears from the 3 pages reproduced from his review that his conclusion is that data available do not provide substantial evidence of a treatment effect. Dr. Leber confirms the widely accepted concept that lithium causes a reversible leukocytosis (an increase in circulating neutrophils), which he terms an innocuous change. Aldous, 9/26/91.

50243-020 (no Record #, but record begins on p. 000204 of this volume) Budd, J.L. and Rossof, A.H., "Drinking water lithium levels fail to predict for the incidences of acute or chronic granulocytic leukemia" (Pritzker School of Medicine of University of Chicago, and Department of Medicine of Rush Medical College, Chicago). in Lithium Effects on Granulopoiesis and Immune Function, Rossof, A.H. and Robinson, W.A., Eds., Plenum Press, NY. (1981). Incidences of acute granulocytic anemia and of chronic granulocytic anemia were plotted against mean drinking water lithium contents in several U.S. cities. There were no indications of treatment effects. Highest levels were 37 µg/L (El Paso), which is likely to be a small contribution to human intake compared to contributions of the diet, especially plant-derived products (see p. 23, this volume). Useful ancillary data. C. Aldous, 9/18/91 (no worksheet was needed or produced for this article).

#### **RAT**

No study on file.

#### **MOUSE**

No study on file.

**REPRODUCTION**

There does not appear to be a justification at present for CDPR to waive the rat reproduction study data requirement, despite the claim on p. 63 of Document 50243-020 that "A vast body of data collected over this period of use indicates that lithium does not pose a reproductive hazard to humans or domestic animals (see Section IV.D)." [Section IV.D. is limited almost entirely to developmental toxicity ("teratology") studies, and does not significantly address male and female reproductive effects to a degree sufficient to warrant a waiver]. Aldous, 10/23/91.

**RAT**

**50243-020 092255** Trautner, E.M., Pennycuik, P.R., Morris, R.J.H., Gershon, S., and Shankly, K.H. "The effects of prolonged sub-toxic lithium ingestion on pregnancy in rats". Austral. J. Exp. Biol. 36:305-322 (1958). (begins on p. 1149 this volume) (Studies were apparently performed at either University of Melbourne and/or University of Brisbane). Female Wistar rats (source not specified) were dosed in drinking water with LiCl (grade, purity, and source not specified) prior to mating with untreated males. Since 50 and 30 meq/l proved lethal to dams (in the latter case, rats survived up to 4 weeks), reproduction studies involved doses of 20 meq/l in water (lower doses were not tested). This dose yielded plasma levels of 1.5 to 2 meq/l (slightly higher than human therapeutic levels), and the only measurable treatment effect on adults was transient (2-3 day) decrements in water consumption. Females were treated for 3 to 7 wk before mating. A number of females were biopsied on about p.c. day 17, and corpora lutea counts were noted to be slightly, but consistently reduced in treated (20 meq/l) groups compared to controls [a **possible adverse effect**]: the length of time on lithium treatment was not a factor (3 wk to 7 wk). No other effects of lithium treatment on reproductive outcome were noted. Study is **not acceptable** and **not upgradeable** due to design limitations. Aldous, 10/2/91.

50243-009 017637 Exact duplicate of **50243-020 092255**, above.

**MOUSE**

**50243-020** (NO RECORD # YET; report begins on p. 001396 of this volume) Mroczka, D.L., Hoff, K.M., Goodrich, C.A., and Baker, P.C., "Effect of lithium on reproduction and postnatal growth of mice", Biol. Neonate 43:287-296 (1983). (Study performed at Cleveland State Univ., Cleveland, OH). CFW mice received drinking water ad libitum with 50 mEq/l LiCl (test article was not further described). In preliminary tests, mice offered 200 mEq/l LiCl failed to drink and soon died, and mice given 100 mEq/l LiCl would not reproduce and appeared to have reduced water intake. Plasma lithium level for 50 mEq/l LiCl mice was determined to average 0.67 mEq/l. Study design involved continuous breeding of groups of 10 pairs of mice at 0 or 50 mEq/l, with treatment either beginning at 6 to 8 weeks (with first mating after 2 weeks), or beginning at 3 weeks of age (with first mating at 8 weeks). Report was confusing to read, but investigators made these conclusions: parental mice did not show toxic effects; among mice treated beginning at 6 to 8 weeks, fewer litters were born to lithium pairs (about 10% longer interval between litters); birth litter sizes were comparable, however pup mortality prior to weaning was twice as high in lithium mice; the incidence of total litter losses was higher in lithium mice; among mice treated beginning at 3 weeks, about a third of litters had delayed growth and development (typically lagging about 1 week by weaning time), with at least some catching up to controls after weaning (when pups were taken off treatment). Study is **not acceptable** (not a standard design), with some useful information. A **possible adverse effect** is indicated (increased pup mortality, delayed growth and development). Aldous, 10/2/91.

**HUMAN CASE HISTORIES**

There are several case reports below. They are typically observations of individual patients, and clearly not rigorously controlled studies. Taken as a whole, these are representative of the reasons for concern about possible reproductive effects of lithium administered at therapeutic levels. The findings reported below were reversible changes in neonates, most or all of which were survivable without medical intervention. It appears that

a modest safety factor could be applied as an interim measure to guard against reproductive toxicity until this data gap is filled. Aldous, 10/07/91.

50243-009 (no record No.: report about mid-way through volume, report was given handwritten serial No. "9") Wilbanks, G.D., Bressler, B., Peete, C.H., Cherny, W.B., and London, W.L., "Toxic effects of lithium carbonate in a mother and newborn infant". JAMA 213:865-867 (1970). A patient receiving monitored lithium therapy (in addition to thioridazine HCl and perphenazine carbonate) delivered an apparently normal baby. The infant soon became cyanotic, and was noted to have "a loud systolic murmur and flaccid muscle tone". The child was placed in an oxygen tent for 2 days. The infant's serum lithium levels were 2.4 and 2.2 mEq/l on the first 2 days, and levels dropped to 0.6 mEq/l on day 13. Cyanosis and murmurs subsided by the third day. Apparently the child was formula fed (i.e., not breast fed). The mother suffered apparent lithium overdose toxicity, despite not having been dosed since at least some hours before the delivery. The mother's serum lithium levels were 3.4 mEq/l on the day of delivery and 4.4 mEq/l two days later. This incident suggests a **"possible adverse effect"** in that normally manageable doses of lithium may lead to overdose (of mother and child) at the time of parturition. Aldous, 10/3/91 (no separate worksheet).

50243-009 (no record No.: report about mid-way through volume, report was given handwritten serial No. "10") Woody, J.N., London, W.L., and Wilbanks, G.D. (Duke University, Durham, NC) "Lithium toxicity in a newborn". This report concerns the same case as summarized above (Wilbanks et al.). The time course of serum lithium levels in the child were presented. The child had serum lithium level of 1.6 mEq/l 7 days after birth (adult toxic level), after which time levels dropped off to well below concentrations of concern. Aldous, 10/3/91 (no separate worksheet).

50243-009 (no record No.: report about mid-way through volume, with serial No. "14" handwritten) Stothers, J.K., Wilson, D.W., and Royston, N.; Br. Med. J. 28 July 1973, pp. 233-234. A mother had been treated daily with 800 mg/day  $\text{LiCO}_3$  during pregnancy (no other drugs). Her blood levels were low during pregnancy (0.20 mEq/l 3 wk before delivery). The newborn child was noted to be hypotonic, and had cord blood serum lithium levels of 0.32

mEq/l. Infant's symptoms included shallow, slightly labored respiration; poor sucking; bradycardia; continuing hypotonia at 10 hr; poorly responsive to handling. Serum levels of infant were 0.38, 0.24, and 0.05 mEq/l at days 1, 4, and 6, respectively. The child improved steadily clinically, and was discharged on the 13th day in good condition. This clinical report was included to suggest that lithium levels below adult therapeutic levels may influence neonatal health. Aldous, 10/7/91 (no separate worksheet).

50243-009 (no record No.: report about mid-way through volume, with serial No. "15" handwritten). Stevens, D., Burman, D., and Midwinter, A.; "Transplacental lithium poisoning". The Lancet, Sept. 7, 1974, p. 595. A woman received 250 mg/6 hr of  $\text{LiCO}_3$  throughout pregnancy. The fetal heart rate was irregular from wk 31 onward. The mother's lithium levels apparently remained at the low end of therapeutic range (0.64 and 0.58 mEq/l at week 21 and 24 hr following delivery, respectively). The child had no apparent distress, despite an altered electrocardiogram, characterized by apparent "retrograde conduction of normal impulses from the A-V bundle". The child's serum lithium level on days 1 and 2 after birth was 0.32 mEq/l. Physicians attributed the temporary EKG abnormalities to lithium because the course of the EKG changes paralleled the elevated child serum lithium, and because lithium has been known to elicit arrhythmias and EKG changes in man and in experimental animals. Aldous, 10/7/91 (no separate worksheet).

50243-009 017630 Schou, M. and Amdisen, A., "Lithium and pregnancy - III, Lithium ingestion by children breast-fed by women on lithium treatment". Br. Med. J. (1973) 21 April, p. 138. Although only limited data were provided, it appeared that a nursing child had about half the lithium concentration of the mother's serum during the first week, and about one-third the mother's serum afterward. Aldous, 10/4/91 (no worksheet, since this is not a FIFRA study, and is not sufficiently current or extensive to warrant a full worksheet).

#### MULTIPLE SPECIES

50243-020 092212 Gralla, E.J. and McIlhenny, H.M. "Studies in pregnant rats, rabbits and monkeys with lithium carbonate". Toxicol. Appl. Pharmacol. 21, 428-433 (1972). Gavage treatment of Charles River rats either before mating, during gestation, or during lactation led to an apparent NOEL of 2.025 meq/kg/day (maternal deaths and diminished weanling weights at 4.05 meq/kg/day). Capsule treatment of New Zealand white rabbits was occasionally fatal to does without apparent effects on offspring (LEL = 1.08 meq/kg/day; apparent NOEL = 0.675 meq/kg/day). Rhesus monkeys were not measurably affected at 0.67 meq/kg/day, the only dose tested. Report is **unacceptable, and not upgradeable** (limited study design does not meet current standards for reproduction or teratology studies, limited detail presented). **No adverse effects were indicated.** See worksheet for details. Aldous, 9/25/91.

50243-009 017642 Exact duplicate of 50243-020:092212, above.

50243-009 017641 MacLeod, J., Swan, R.C., and Aitken, G.A., "Lithium: Its effect on human spermatozoa, rat testicular tissue and upon rats in vivo", Amer. J. Physiol. 157:177-183 (1949). Study was performed at Cornell University Medical College, Departments of Anatomy and Medicine. Human sperm were suspended in Ringer-glucose solution and assessed for motility and for glycolytic activity (lactate production) at lithium concentrations of 6, 12.5, or 25 mM lithium. Glycolytic activity was reduced in dose-related manner, with a 40% reduction in the highest concentration. It was noted that substantially higher lithium concentrations did not elicit proportionately greater inhibition of glycolysis. Sperm motility (% active at 4 hr) was 50%, 36%, 10%, and 2% in controls through 25 mM Li concentrations, respectively. Rat testicular tissue was also incubated in a Warburg apparatus, to evaluate aerobic and anaerobic glycolytic activity. The only change was in aerobic glycolytic activity, and the effect of lithium in concentrations of 10 to 1000 mM was dose-related increased glycolysis. In a rat breeding study, males were dosed with 1, 3, 5, 10, or 15 mg lithium/day subcutaneously for up to 14 days (2 to 3 rats/group: rats weighed 270 to 300 g in most cases). Males were then placed with proven fertile females. Doses up to 3 mg/day did not elicit toxicity nor affect fertility (males sired normal litters). Toxic signs apparently observed at 5 mg/day and up were "reflex excitability followed by paralysis of hind limbs". At 5 mg/kg, two of 3 males showed toxic signs, and only one of these mated and sired 2 normal litters. All males administered 10 to 15 mg/day showed toxic signs, and only one of the 5 rats at these higher doses sired a litter. Two of 3 of the 15 mg/day rats died due to treatment, and the three survivors in the 10 to 15 mg/day range appeared to be too weak to mate. Histological sections of germinal epithelia of testes of these rats were examined, and all appeared "normal with an abundance of mature spermatozoa in the tubules". Since the in vivo study provided an apparent NOEL of about 10 mg/kg/day (compared to human therapeutic oral doses of about 3 mg/kg/day), and since the in vitro inhibition of human sperm was noted only at concentrations higher than survivable human plasma levels, the study is not considered to represent a "possible adverse effect". Aldous, 10/3/91.

#### TERATOGENICITY



NOTE: As indicated on the cover page of this Summary, two lithium salts have been "listed" as reproductive toxins under California "Proposition 65".

009 Several published articles and excerpts from books were submitted for teratology studies. Many of them deal with human exposure; lithium, pregnancy and the newborn are identified with record numbers as follows:

017620	017623	017624	017625	017626	017627	017628
017629	017630	017631	017632	017633	017634	035810

and those which deal with mammals other than man are identified with record numbers as follows:

017621	017635	017636	017637	017638	017641	017642
035807	083508	083509	083511	083512		

None of the articles with record numbers listed above can fill the teratogenicity study data requirement. (Above analysis was probably part of the 3/89 Summary). An acceptable rat teratology study using lithium hypochlorite has since been evaluated (below). **The remaining data gap can be filled by a second mammalian species, probably the mouse.** It would seem unlikely that human data from mothers on lithium therapy would fill this data requirement, since expectant mothers are generally advised to avoid lithium during at least the first trimester. Update by Aldous, 10/23/91.

EPA one-liner: Supplementary. Lithium salts have the potential for producing terata and fetotoxicity in both animals and man.

50243-020 092257 Warkany, J., "Teratogen update: Lithium", Teratology 38:593-596(1988). [pp. 1171-1174 in part 2, Vol. 20]. Brief overview of major publications regarding human developmental risks associated with lithium. The major concern about lithium is the possibility that Ebstein's anomaly (a misplaced tricuspid valve) appears in some

epidemiological analyses to be increased in babies of mothers who took lithium during the first trimester. The author concluded that lithium therapy "is contraindicated in women of reproductive age unless pregnancy is prevented." This article is included because it is a relatively recent review by a U.S. pediatrician, and appears to be representative of the caution recommended by health care professionals regarding lithium use (in therapeutic doses) during pregnancy. No Medical Toxicology Branch review is appropriate, nor does this overview provide a numerical basis for risk assessment. Aldous, 9/24/91.

#### TERATOGENICITY, RAT

**NOTE:** There are several rat studies below which indicate "possible adverse effects". Clearly the most relevant study, however, for lithium hypochlorite hazard assessment is the 1988 Argus study which follows. That study is negative, and involves the most defensible route and test article: also, the study follows current FIFRA guidelines. For this reason, the hazard assessment for teratology in the rat **does not** consider the collective data in rats to constitute a "possible adverse effect", despite several "unacceptable" studies which were flagged as having "possible adverse effects". Aldous, 10/8/91.

\*\*50243-016 068353 Lochry, E.A., "Developmental Toxicity (Embryo/Fetal and Teratogenic Potential) Study of Lithium Hypochlorite Administered orally Via Gavage to Crl:CD\* (SD)BR Presumed Pregnant Rats", (Argus Research Laboratories, Inc., ARLP no. 106-004, 4/18/88). Test article was a white granular powder containing approximately 29% lithium Hypochlorite, was administered by gavage at concentrations of 0 (deionized water), 10, 50, 100 or 500 mg/kg/day to 25 Charles River Crl:CD\*(SD)BR female rats/group on days 6 through 15 of gestation. Maternal NOEL = 100 mg/kg/day. Findings included increased mortality, often preceded by chromorhinorrhea, chromodacryorrhea, labored breathing, and/or urine-stained abdominal fur. Inflamed or congested lungs were observed at necropsies of these dams. High dose dams also had statistically significant decrements in body weight gains and in food consumption during the treatment period. Developmental NOEL = 100 mg/kg/day [decreased fetal weight (significant in females only), wavy ribs, thoracic bifid centra, ossification delays in

forepaw phalanges and metatarsals]. **No adverse effects. Acceptable.** Kishiyama and Aldous, 8/28/91.

**50243-020 092256** Tuchmann-Duplessis, H. and Mercier-Parot, L., "Teratologie: Influence of lithium on the gestation and prenatal development of the rat and the mouse", C. R. Soc. Biol. 167:183-186 (1973). Universite' Rene' Descartes, Paris. [A narrative without extensive detail]. LiCl (grade not specified) was injected ip into Wistar rats (most commonly on days 1-12 or 7-11) at doses of 0, 100, 150, 200, or 250 mg/kg/day. Examination methods were not specified. The only definitive (apparently dose-related) maternal effect in rats was mortality (4/9 at 250 mg/kg/day: no mention of toxicity at lower doses). The only anomalies noted in rat fetuses were some kind of ocular malformation (not further described in text, and photocopies of figures showing examples are not readable), which were observed occasionally at 150 to 200 mg/kg/day, and more often (15% fetal incidence) at 250 mg/kg/day. In Swiss-derived mice, 250 mg/kg/day was uniformly lethal to dams, and 100 to 150 mg/kg/day did not exert developmental effects. Rat data suggest a "**possible adverse effect**", limited to the range of maternal toxicity. Study is **unacceptable, and not upgradeable** (design limitations), limited useful data. Aldous, 9/13/91 (no worksheet, since a study by a more appropriate route is available).

**50243-020 092260** Wright, T.L., Hoffman, L.H., and Davies, J., "Teratogenic effects of lithium in rats", Teratology 4:151-156 (1971). Vanderbilt Univ. School of Medicine, Nashville TN. LiCl (grade not specified) was injected ip into Sprague-Dawley rats (weighing 220-250 g), beginning on gestation day 1, 4, 7, or 9: only 3 rats per group. First dose for each group was 50 mg, then 20 mg/day daily through day 16. (Regimen was considered the "maximum sublethal doses"). Dams were killed day 17, and all fetuses were examined superficially. "Some fetuses" (method of selection was not specified, however 115 fetuses were examined from among the 12 litters) were further examined for soft tissue changes. **Possible adverse effects:** major findings were (1) eye defects in 63% of fetuses (ventromedial displacement of eye in most cases: unilateral agenesis in 4 cases, all of the latter being in groups started on day 4); (2) external ear defects in 45% of fetuses, marked by "failure of the auricular hillocks to fuse properly"; and (3) cleft palate in 39% of fetuses (ranging from complete

cleft palate to bifid soft palate). Except for the eye agenesis, none of the effects seemed to vary with treatment starting dates. Study is **not acceptable, and not upgradeable** (limited design, not optimal route of dosing). Aldous, 9/13/91.

**50243-020 092238** Marathe, M.R. and Thomas, G.P. "Embryotoxicity and teratogenicity of lithium carbonate in Wistar rat", Toxicol. Lett. 34:115-120 (1986). [begins p. 001025 in part 2, this vol.]. IDPL Research Centre, Hyderabad, India. In-house-bred Wistar rats were dosed by gavage with lithium carbonate [grade and purity not specified, however material was suspended in 0.2% agar] on days 6-15. Dams were sacrificed on day 20, and about 1/3 of fetuses were examined for visceral changes, with the balance being examined for skeletal effects. Treatment groups were controls (n = 20), 50 (n = 13) and 100 mg/kg/day (n = 11). Investigators indicated that in-house studies had found 200 mg/kg/day caused "toxic effects and mortality". This report did not discuss whether there were evidences of maternal toxicity or weight gain effects at 50 or 100 mg/kg/day. Apparent developmental effects NOEL = 50 mg/kg/day. The following treatment effects were observed at 100 mg/kg/day: marked reduction of live pups/litter [associated with significant (p < 0.01) reduction of implantations, and non-statistically (but possibly biologically) significant increases in early and late resorptions. Body weights of 100 mg/kg/day fetuses were reduced to 2/3 of control weights. Other treatment effects at 100 mg/kg/day were ossification delays in sternebrae, delayed fusion of bones in skull, long bones in extremities notably shortened, wavy ribs, and deformities (not further described) of the scapula and pelvic bones. Data indicate a **possible adverse effect**, however the value of this study is limited by (1) lack of data on maternal toxicity at 100 mg/kg/day, (2) small treatment group sizes, and (3) lack of details on certain study design features. The apparent NOEL of 50 mg/kg/day suggests that this study is not a priority item for eventual risk assessment. **Unacceptable, not upgradeable.** Aldous, 9/27/91.

#### RABBIT

No studies on this species with sufficient detail for independent review.

## MOUSE

**50243-020 092251** Smithberg, M., and Dixit, P.K., "Teratogenic effects of lithium in mice", Teratology 26:239-246 (1982). Univ. Minnesota Medical School, Minneapolis, MN. Lithium carbonate (analytical grade) was administered to strains 129 and A/J mice. Most dosing was ip, typically doses of 0.8, 1.6, 3.2, or 5.0 mg lithium CO<sub>3</sub> [the latter being approx. LD<sub>50</sub>], usually given on single days (most extensive dosing on days 8-10). Also, strain 129 mice were dosed via drinking water containing 2 mg/ml lithium CO<sub>3</sub> on days 1-18. Fetal exams were limited to external and skeletal inspections. The lower ip doses and the Li-treated water administration were stated to provide peak serum levels in the range of human therapeutic levels, i.e. about 1 meq/L. In strain 129, ip dosing with 5 mg/mouse led to increased numbers of abnormalities following injection on day 8, 9, or 10: common defects were "fused ribs and/or vertebral defects and exencephaly". Percent resorptions appeared to be increased at that dose. Other ip dose groups of this strain were apparently unaffected. Reduced numbers of litters and increased % resorptions were characteristic of the strain 129 mice dosed in drinking water. There were no characteristic abnormalities elicited in the A/J mice, however there were reduced numbers of litters in day 8 and day 9 mice dosed with 1.6 mg/mouse or above. Investigators interpreted results as indication that therapeutic doses did not elicit developmental effects, although doses near to the LD<sub>50</sub> did elicit such effects. Nevertheless, serum lithium levels fell to about 50% of peak concentrations by about 4 hr after dosing, suggesting that duration of exposure following ip dosing might be shorter than following oral dosing. **Not acceptable nor upgradeable** (fundamental design limitations), some useful data. Aldous, 9/5/91.

**50243-020 092253** Szabo, K.T., "Teratogenic effect of lithium carbonate in the foetal mouse", Nature 225:73-75 (1970). Smith Kline and French Laboratories, Philadelphia, PA. Randomly bred HaM/ICR mice were dosed by gavage (in tragacanth gel) once daily on days 6-15 of pregnancy. Fetuses were examined externally, and then some were examined for soft tissues and others for skeletal effects. A pilot study had indicated increased cleft palate at 300 and 465 mg/kg/day lithium carbonate (only 3-4 litters/group). The main study involved only 200 and 465 mg/kg/day groups, yielding 20 and 15 litters, respectively. Sixteen percent of 465

mg/kg/day fetuses had cleft palate (back palate only: 47% of litters were affected). Reported maternal deaths and embryonic/fetal resorptions at 465 mg/kg/day were 37% and 32%, respectively. There were no maternal deaths, fetal abnormalities, nor increased resorptions at 200 mg/kg/day (the apparent NOEL). High dose average lithium serum levels were about 2 meq/l, just above human therapeutic range (and into a recognized toxic range in humans). Data indicate a **possible adverse effect**. Study is **not acceptable** to fill a data requirement (design limitations: not upgradeable), but has some useful data. Schreider, 3/22/85 (as Vol. 009, Record 017640), Aldous, 9/6/91.

50243-009 017640 Exact duplicate of **50243-020 092253**, above.

009 017639 Preliminary data/notes on study 017640

**50243-020 092235** Loevy, H.T., "Lithium ion in cleft palate teratogenesis in CD<sub>1</sub> mice". Proc. Soc. Exper. Biol. Med. 114:644-646 (1973). Department of Pedodontics, Univ. of Illinois, Chicago. [begins p. 000985, Part 2, this vol.] Mice were injected subcutaneously with 15.5 mg LiCl monohydrate. Grade or purity of test article were not given, nor were weights of dams. Ten dams per group were injected on days 11 and 12, 12 and 13, or 11-13. Investigators noted no maternal toxicity. Dams were sacrificed on day 17, and fetuses were examined for cleft palate and other gross malformations. Percent cleft palate was 3.4%, 7.2%, and 15.1% for the above 3 groups, respectively (a **possible adverse effect**); vs. 0.5% in untreated plus vehicle controls. (Respective litter incidences were 3, 4, and 6 in the 3 treated groups). The study is unacceptable (inappropriate dose route, insufficient group sizes, only one dose level, limited evaluation of fetuses) and was not designed to meet FIFRA requirements. Study provides limited useful information (it is consistent with other studies showing potential of lithium to cause cleft palate in mice at high doses by various routes). Aldous, 9/27/91.

#### HUMAN EPIDEMIOLOGICAL DATA

50243-020 092229 Källén, B. and Tandberg, A., "Lithium and pregnancy: A cohort study on manic-depressive women", Acta Psychiatr. Scand. 68:134-139 (1983). [beginning on p. 000682, this volume]. 350 Swedish women who had at least once been treated for manic-depressive disease and who had born a child were evaluated vs. expected numbers (based on all births in Sweden). Two outcomes were significant ( $p < 0.05$ ): "total perinatal deaths" 9 [4.3 expected], and "heart defects" [2.1 expected]. Of the heart defects, 4 were infants born to the group of 59 mothers who received lithium. There were no cases of Ebstein's anomaly in the test sample. Other factors noted were higher maternal age in test sample than typical of the Swedish population, and appreciably higher percent of smoking during early pregnancy among women treated with lithium or women treated with other psychotropic drugs compared to the control women. Data were considered to warrant avoidance of lithium therapy during early pregnancy, however investigators recommended that a larger cohort study be undertaken. [No worksheet, since this is not a FIFRA-mandated study]. Aldous, 9/26/91.

50243-020 092287 Schou, M., Goldfield, M.D., Weinstein, M.R., and Villeneuve, A. "Lithium and pregnancy - I, Report from the Register of Lithium Babies". Br. Med. J. (1973) 21 April, pp. 135-136. An early birth registry report of outcomes of 118 births in Scandinavia. These births were to mothers who had been treated with lithium during the first trimester. There were 5 stillbirths (one of which was malformed), and 7 infants which died within one week after birth (5 of these were malformed). An additional infant died 2 weeks after birth. A total of 9 infants were malformed. Two were Down's syndrome. Six malformations involved the cardiovascular system. The report does not indicate expected numbers of stillbirths nor of malformations, however it is clear from the investigators' discussion that these incidences were above general population expected values. Investigators consider that a retrospective study such as this tends to over-represent abnormal outcomes [especially with respect to reports originating outside Scandinavia, which encompassed many of the malformations and stillbirths], since there is less incentive to report a normal birth to the registry than there is to report a malformation. [This report is probably of little value for risk assessment, but highlights the need for careful review of much more extensive and validated epidemiology data]. Aldous, 10/4/91 (no worksheet, since this is not a FIFRA study, and is not sufficiently current or extensive to warrant a full worksheet).

50243-020 092228 Källén, B., "Comments on teratogen update: Lithium". Teratology 38:597 (1988). P. 000681 of this volume. Epidemiological data were provided which do not support association between lithium exposure and cardiac abnormalities. An international joint case-control study had 69 case infants with Ebstein anomaly (25) or tricuspidal atresia (44), vs. 128 controls having no cardiac defects. Although all cases came from countries in which lithium was used for manic depressive illness, none of the mothers of children with these heart defects had been exposed to lithium. An additional French study identified a group of 15 cases of Ebstein anomaly. Drug histories had been monitored on these mothers, and none of these had lithium use histories. [No worksheet, since this is not a FIFRA-mandated study]. Aldous, 10/9/91.

50243-020 092226 Johnson, E.M. "The developmental toxicity of lithium". A recent (6/28/89) review of human and animal studies, beginning on p. 000641. Most valuable in the present context for the summaries of the major studies, which follow his review. Aldous, 10/9/91.

#### GENE MUTATION

\*\* 50243-015 066107, "CHO/HGPRT Mutation Assay", (L. L. Yang, Microbiological Associates Inc., MBA Study No. T5674.332005, 1/27/88). CHO cells were exposed for 5 hours to lithium hypochlorite (lot 408-238) concentrations of 100, 140, 180, 220, or 260 µg/ml in the absence of S-9 and at 250, 425, 550, 625 or 675 in the presence of rat liver S-9 and then repeated with a confirmatory assay. The confirmatory assay did not reproduce a statistically significant concentration-related (675 µg/ml) increase in mutation frequency; therefore, no mutagenic effect is indicated. ACCEPTABLE. (Kishiyama and Gee, 9/13/91)

\*\* 50243-015 065965 "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test).", (K. J. Batt, FMC Corporation, Toxicology Dept., Lab Project Study No. I87-0975, 12/16/87). Lithium hypochlorite (lot 408-238, 36.6 wt % available chlorine, 4.1 wt % lithium) at concentrations of 5, 16.7, 50, 167, or 250 µg/plate and at 5, 16.7, 50, 167 or 500 µg/plate without and with Aroclor-induced rat liver (S-9) mix, respectively, were plated with



Salmonella tester strains, TA1538, TA1537, TA1535, TA100 and TA98. The first and confirmatory assays included additional lithium hypochlorite doses at 1.67 µg/plate and at 67 and 100 µg/plate without S-9 mix, respectively. Lithium hypochlorite treatments did not cause an increase in the number of revertants and therefore, considered non-mutagenic. ACCEPTABLE. (Kishiyama and Gee, 9/13/91)

#### CHROMOSOME

\*\* 50243-015 066210, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells", (D. L. Putman, Microbiological Associates Inc., Lab. Study No. T5674.337020, 2/3/88). Lithium Hypochlorite (lot 408-238, 36.6 wt % available chlorine, 4.1 wt. % lithium) was tested at concentrations of 15, 30, 60 and 120 µg/ml non-activated and at 25, 50, 100 and 200 µg/ml with Aroclor 1254-induced rat liver S-9 activation with Chinese Hamster Ovary Cells. The non-activated and S-9 activated high dose groups showed a statistically significant increase of chromosome aberrations at 12 hours. With activation, aberrations per cell and % cells with aberrations were also increased at 25 and 50 but not at 100 µg/ml; therefore, no clear dose response. The mitotic indices were lower at the high concentrations at 12 hours, especially. The results are not clear-cut. Fifty spreads from each of the duplicate cultures were scored. ACCEPTABLE with a possible adverse effect. (Kishiyama and Gee, 9/12/91)

\*\* 50243-019 070810, "Acute In Vivo Cytogenetics Assay in Male and Female Rats", (D. L. Putman, Microbiological Associates Inc., Lab. Study No. T8108.105004, 11/3/88). Lithium Hypochlorite (lot 408-238) was given as a single dose by gavage at concentrations of 100, 500, or 1000 mg/kg to 5 male Sprague-Dawley rats/group and at 50, 250, or 500 mg/kg to 5 female Sprague-Dawley rats/group. Potential for chromosomal damage was measured in the bone marrow at 6, 24 and 48 hours after dose administration. Study reports no chromosomal aberrations induced in the bone marrow of rats. ACCEPTABLE. (Kishiyama and Gee, 9/13/91)

50243-020 092221 "Chromosome Examinations in Patients on lithium Carbonate." (Jarvik, L. F., N. P. Bishun, H. Bleiweiss, T. Kato and E. Moralistvili; New York State Psychiatric Institute, 1971) Sixteen patients on lithium carbonate therapy for two weeks to over two

years were compared with 4 patients on placebo and 10 "drug-free" controls. Ages of patients ranged from 30 to 73 years. The serum level of lithium was determined the same day as the leukocyte cultures were initiated. Seventy-two hour cultures were harvested. For the last two hours, demecolcine was added. Cells were scored for number of chromosomes and abnormalities. No statistically significant differences between controls and patients were found. The authors state the sample sizes were too small to prove a lack of differences between the groups. **No adverse effect indicated. Unacceptable.** Gee, 10/18/91.

50243-020 092206 "Study by Foote Mineral Company demonstrating that the proposed final effluent limits for lithium and bromide are not necessary to protect human health." (Jacobson, R. N., et. al., 8/19/85) An overview on lithium including a section on potential for mutagenic effects. The authors conclude that there is "no reliable evidence of mutagenic effects of lithium even at therapeutic levels...." Quote from page 000331. No worksheet. Gee, 10/21/91.

50243-020 092206, Appendix E "Potential mutagenic hazard associated with lithium exposure." (D. J. Brusick, no date) A review of the non-human and human studies conducted with lithium and the outcome of each study is contained in the document. The author concluded that the few studies showing positive effects in publications from the open literature were not adequately performed or controlled. The greater number of studies were negative. No worksheet. Gee, 10/21/91.

Summary: Based on the weight of evidence, lithium is not considered to pose a genotoxic problem. Gee, 10/21/91.

#### DNA DAMAGE

\*50243-015 066167, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes", (R. D. Curren, Microbiological Associates Inc., Lab Study No. T5674.380017, 1/11/88). Rat hepatocytes received 18-20 hours exposure to lithium hypochlorite (lot 408-238) concentrations of 0 (WME), 1.5, 5, 15, 50 150, 250, 350 or 500 µg/ml. Cell survival averaged >95%, 85% and <20% for the

three lowest doses, 150 µg/ml dose and the three highest doses, respectively. The count of silver grains for lithium hypochlorite treatments did not show a statistically significant increase compared to the solvent control. ACCEPTABLE. (Kishiyama and Gee, 9/10/91)

#### NEUROTOXICITY

Not required at this time.

No study on file.

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Note: Medical Toxicology Branch recognizes that much of the data presented by Lithium Corporation of America derive from therapeutic exposure, which is indicated to be about two orders of magnitude higher than exposure to the general population. Two items of information, neither of which is required under auspices of California Senate Bill 950, would appear to be relevant to understanding lithium exposure due to proposed uses vs. background exposure. One is the characterization of dietary intake of lithium in foods. The scant data submitted so far indicate appreciable exposure from leafy vegetables in the diet, for example, however the extent and variability of such exposure (perhaps very dependent on the soil and water characteristics where such crops are grown) was not presented. The second type of information relates to general human body burden of lithium, usually measured in blood. Widely varying background human serum lithium concentrations have been reported over the years by different investigators. Systematic measurement errors have been implicated, often with respect to older studies, in some of the reviews. Neither of these items affects the acceptability of studies for filling data gaps under SB-950. Aldous, 10/23/91.